R E M A R K S

Reconsideration of this application, as amended, is respectfully requested.

THE CLAIMS

Claim 1 has been amended to recite that the range of parameters of the ultrasound waves being directed from the multiple transducers focused at the location are selected in order to _induce_ cavitation, so as to overcome the rejection under 35 USC 112, second paragraph.

It is respectfully submitted that the amendment to claim 1 is clarifying in nature only and that no new issues have been raised which require further consideration on the merits and/or a new search. Accordingly, it is respectfully requested that the amendment to claim 1 be approved and entered under 37 CFR 1.116, and that the rejection under 35 USC 112, second paragraph, be withdrawn.

THE PRIOR ART REJECTION

Claims 1-3, 8-11, 15 and 17 were rejected under 35 USC 102 as being anticipated by USP 5,827,204 ("Grandia et al"). In addition, the remaining claims were rejected under 35 USC 103 as being obvious in view of various combinations of Grandia et al with one or more of USP 6,508,774 ("Acker et al"), USP 5,219,401

("Cathignol et al"), USP 6,413,216 ("Cain et al"), USP 4,618,831

("Egami et al"), and US 2002/0009015 ("Laugharn et al"). These

rejections, however, are respectfully traversed.

On pages 11-12 of the Final Office Action, the Examiner

asserts (with respect to claim 1) that Grandia discloses

"selecting a range of parameters of the ultrasound waves to

improve cavitation". In particular, the Examiner asserts that

Grandia et al discloses "carefully chosen parameters for

controlling and optimizing the effect of cavitation in a region

[see column 2 lines 42-44]; the dimension of focal zone may be

controlled by selecting a curvature of the focused modulated high

power transmitter and the high frequency value [see column 6

lines 33-35]."

In addition, at the middle of page 12 of the Final Office

Action, the Examiner asserts (with respect to claim 1) that

Grandia et al discloses "simultaneously directing ultrasound

waves from the transducers". In particular, the Examiner asserts

that Grandia et al discloses "a transmitter 18 that may comprise

a combination of transducers, or a single focused transducer 56

which is driven to produce simultaneously two or more frequencies

in, such as the high frequency signal 34 and low frequency

signals 32, in either continuous or tone burst mode [see column 7

lines 40-50]" and that Grandia et al also discloses that "a low

power ultrasonic field is transmitted through the medical target

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area in order to produce a visual image of the area being treated. This may be accomplished, for example, by use of an array transducer ultrasonic imaging system, such as Model UT-3D (QMI, Costa Mesa, Calif.) or by use of a high frequency ultrasonic transducer 66b, forming a part of an imaging axicon transmitter and receiver, which produces a pencil shaped, low power high frequency ultrasound field in the medical target region [see column 7 lines 26-34]."

Applicant respectfully disagrees.

It is respectfully pointed out that a short duration pulse of an ultrasound pressure wave, traveling through an ideal linear liquid, would <u>not</u> produce cavitation. This is because negative pressure tends to produce microbubbles, while positive pressure tends to impede the production of microbubbles. In addition, it is noted that rectified diffusion facilitates cavitation and increases the size of the microbubbles - when pulse sequences of longer duration are used. The non-linear behavior of oscillating microbubbles and the non-linear behavior of liquid/tissue require that in order to efficiently generate microbubbles at a specific location, the shape of the ultrasound pressure wave at that location should be controlled.
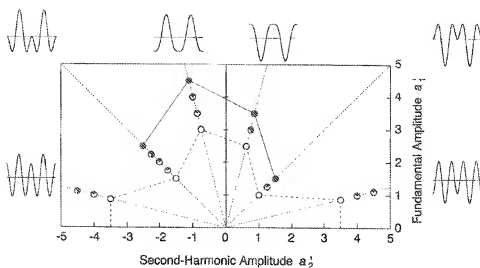
The generation of cavitation in liquid or tissue by ultrasound waves or pressure depends mostly on the peak negative pressure (which enhances cavitation), the peak positive pressure

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(which decreases generation of cavitation) and frequency (where lower frequency enhances generation of cavitation). There are other parameters of less importance that affect this process (e.g., the duration of the ultrasound insonation, and the liquid/tissue properties and the amount of gases dissolved in it, that affect the cavitation threshold).
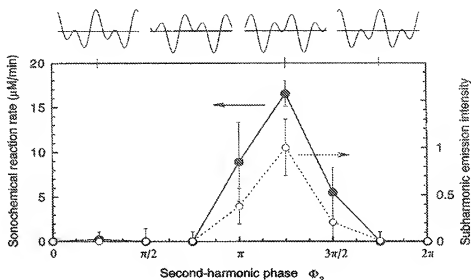
There are two fundamental studies that describe, using theory and experimental work, the relationship between these key parameters (i.e., peak negative pressure, peak positive pressure, and frequency): "Enhancement of Sonodynamic Tissue Damage Production by Second-Harmonic Superimposition: Theoretical Analysis of Its Mechanism" ("Umemura et al '96"), and "*In Vitro* and *in vivo* enhancement of sonodynamically active cavitation by second-harmonic superimposition" ("Umemura et al '97").[1]

In Umemura et al '96, it is demonstrated that the highest probability of generating cavitation occurs when the waveshape is generated by the combination of the fundamental amplitude and second-Harmonic amplitude that are both ~1, but only with the right phase, which produces an asymmetric US field with a larger negative pressure amplitude than the positive pressure amplitude, at the required location. See in particular Fig. 8 of Umemura et al '96, reproduced below for the Examiner's convenience.

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[1] These references were listed in the IDS filed November 24, 2008.

In addition, in Umemura et al '97, it is clearly demonstrated that only when the 2nd harmonic phase is accurately set versus the Fundamental harmonic ($5\pi/4$), the probability of generating cavitation is significantly higher. See Fig. 5 of Umemura et al '97, reproduced below for the Examiner's convenience.

It is respectfully submitted that it is not at all obvious from the disclosure in Grandia et al how to combine two pressure waves at their focal point, so that at this point the probability of generating cavitation is greater than that provided by each wave alone. That is, it is respectfully submitted that Grandia et al does not disclose or suggest simultaneously directing ultrasound waves from multiple transducers at a location at which the transducers are focused and selecting a range of parameters of the ultrasound waves in order to induce cavitation and to produce from interference of the ultrasound waves at that location a specific waveform, as according to the present invention as recited in amended independent claim 1.
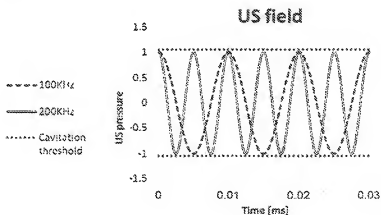
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Following Grandia et al, an example of two waveforms, one at 100kHz and the second at 200kHz, is discussed below:

$$P_1(t) = A\cos(wt + \varphi_1)$$
$$P_2(t) = A\cos(2wt + \varphi_2)$$

where $P_1(t)$ and $P_2(t)$ represent the pressure of the two waves at their natural conjoint focal point, $w = 2\pi \times 100{,}000$ [1/sec], and φ_1 and φ_2 are the initial phases (when $t=0$), and wherein it is assumed that A is below the cavitation threshold at 100kHz, and that, for example, $1.1A$ is above the threshold (i.e., the threshold is, for example, at $1.05A$). See Reference Figure 1, below.

Figure 1:

US field

– – – 100KHz		
——— 200KHz		
······· Cavitation threshold		

US pressure

1.5
1
0.5
0
-0.5
-1
-1.5

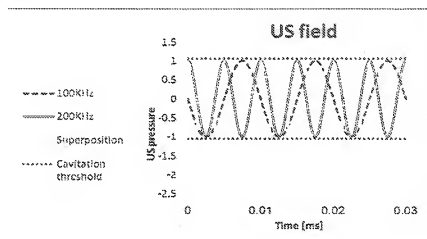0   0.01   0.02   0.03
Time [ms]

The waveform, generated by the superposition of two waves, depends on three parameters: the phases at each specific location, the relative amplitudes, and the frequency ratios between these waves. $\bar{A}$ = *(NegativePeak - PositivePeak)*/ 2 is defined as the average amplitude of this combined waveform, which might be symmetric or asymmetric.

It has been shown experimentally (see above Fig. 8 of Umemura et al '96 and Fig. 5 of Umemura et al '97) that when two waveforms are combined, cavitation occurs when $\bar{A}$ x *(NegativePeak/PositivePeak)* exceeds the threshold. Since the negative peak to positive peak ratio strongly depends on the wave phases, which are spatial point dependent, the initial phases (φ_1 and φ_2) must be aligned properly in order to provide the required condition for cavitation in the required location (according to the distance the beam waves pass from the transducer to the specific point).

Reference Figure 2 is an example for which $\varphi_1=90°$, $\varphi_2=0°$ and A1=A2=0. In this case, the two waves are indeed combined, such that the addition of the second waveform enhances cavitation at the conjoint focal point. See below.
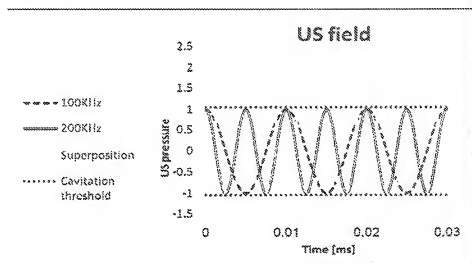
Figure 2:

It is respectfully pointed out that Grandia et al wrongly
teaches that in any case of superimposing waves the probability
for cavitation is increased regardless of any specific required
phases, amplitudes, or frequencies. (In this connection, it is
noted that the case of using 100kHz and 200kHz in Grandia et al
was discussed therein only as an example).

Reference Figure 3 is an example for which $\varphi_1 = \varphi_2 = 0°$ and
A1=A2=1. In this case, although the negative peak and the
positive peak exceed the threshold, the probability for
generating cavitation at the conjoint focal point is actually
decreased due to the negative peak to positive peak ratio.
See Reference Figure 3 below.

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Figure 3:

It is respectfully pointed out that Grandia et al wrongly teaches that in this case also the probability for cavitation is increased. And it is again respectfully submitted that Grandia et al fails to teach the selective production of cavitation or of heating in a small zone, obtained in part by a high frequency component, as according to the claimed present invention.

In view of the foregoing, it is respectfully submitted that Grandia et al does not disclose or suggest simultaneously directing ultrasound waves from multiple transducers at a location at which the transducers are focused and selecting a range of parameters of the ultrasound waves in order to induce cavitation and to produce from interference of the ultrasound

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waves at that location a specific waveform, as according to the present invention as recited in amended independent claim 1.

And it is respectfully submitted that the present invention as recited in amended independent claim 1 and claims 2-37 depending therefrom clearly patentably distinguishes over Grandia et al, taken singly or in combination with any of the other prior art references of record, under 35 USC 102 as well as under 35 USC 103.

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Entry of this Amendment, allowance of the claims and the passing of this application to issue are respectfully solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned for prompt action.

Respectfully submitted,

/Douglas Holtz/

Douglas Holtz
Reg. No. 33,902

Frishauf, Holtz, Goodman & Chick, P.C.
220 Fifth Avenue - 16th Floor
New York, New York 10001-7708
Tel. No. (212) 319-4900

DH:bl